RAPID DIAGNOSTICS

Utility of the Determine Syphilis TP rapid test in commercial sex venues in Peru

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Objectives: This study sought to evaluate the utility of the Determine Syphilis TP test performed in Peruvian commercial sex venues for the detection of active syphilis; and determine the feasibility of integrating rapid syphilis testing for female sex workers (FSW) into existing health outreach services.

Methods: We tested 3586 female sex workers for syphilis by Determine in the field using whole blood fingerstick, and by rapid plasma reagin (RPR) and *Treponema pallidum* haemagglutination assay (TPHA) in a central laboratory in Lima using sera.

Results: 97.4% of the FSW offered rapid syphilis testing participated; and among those who tested positive, 87% visited the local health centre for treatment. More than twice as many specimens were RPR reactive using serum in Lima (5.7%) than tested positive by whole blood Determine in the field (2.8%), and although most were confirmed by TPHA, only a small proportion (0.7%) were RPR reactive at ⩾1:8 dilutions, and likely indicating active syphilis. Sensitivity, specificity and positive predictive value of the Determine Syphilis TP test in whole blood when compared to serum RPR reactivity at any dilution confirmed by TPHA as the gold standard were 39.3%, 99.2% and 71.4%, respectively. Sensitivity improved to 64.0% when using serum RPR ⩾1:8 confirmed by TPHA. Invalid tests were rare (0.3%).

Conclusions: Rapid syphilis testing in sex work venues proved feasible, but Determine using whole blood obtained by fingerstick was substantially less sensitive than reported in previous laboratory-based studies using serum. Although easy to perform in outreach venues, the utility of this rapid syphilis test was relatively low in settings where a large proportion of the targeted population has been previously tested and treated.

Syphilis seroreactivity rates in the Peruvian general population range from 1.1% among young adults sampled through a household-based survey[1] to 7.7% among high risk adults recruited through community-based entertainment venues.[2] Reported seroreactivity among female sex workers (FSW) in Peru has ranged from 3% among unlicensed, brothel-based FSW in Lima[3] to 6% among FSW in sex work settings across the country.[4] In concentrated HIV/sexually transmitted infections (STI) epidemics, such as those in Latin America, it is critical to prevent and treat infection in core groups, such as FSW, to restrict disease transmission into the general population.[5] Although the Peruvian Ministry of Health HIV/STI Control Program (PROCETSS) offers screening services that are specifically designed for sex workers, less than a quarter of the estimated number of FSW access this clinic-based health care, highlighting the need for field-based testing and treatment for this vulnerable population.

The development of rapid diagnostic tests for sexually transmitted infections (STIs) presents an opportunity to implement screening and treatment services in low-resource settings, where laboratory facilities are not always available, and in non-clinical settings where individuals who do not access standard health care services can be reached.[6] There are currently over 20 different rapid syphilis tests on the market, with varying levels of performance.[7] Based on published evaluations and ease of use, we selected the Determine Syphilis TP rapid test (Abbott Laboratories, Tokyo, Japan) to screen FSW for syphilis.

With all previous studies conducted in laboratory and clinical settings, we sought to: (1) evaluate the utility of the Determine Syphilis TP rapid test for the detection of active syphilis when used in a field-based setting comprised of commercial sex venues; and (2) assess the feasibility of integrating rapid syphilis testing into existing health outreach services.

METHODS

This evaluation was nested within the PREVEN project, an ongoing community randomised trial of STI prevention in 20 mid-sized cities in Peru. In this three-year hybrid intervention aimed to reduce prevalences and incidence of syphilis, gonorrhoea (GC), chlamydial infection (CT) and trichomoniasis (TV) among female sex workers and the young adult general population, PREVEN mobile outreach teams visit commercial sex venues every eight weeks to offer STI screening and treatment services in the 10 trial intervention cities.[8] Comprised of a health worker, a counsellor and a peer FSW outreach worker, each mobile team offers presumptive metronidazole treatment for vaginal infections, provides and promotes condoms, and obtains self-collected vaginal swabs for central CT/GC testing by polymerase chain reaction (PCR) and local TV in-pouch culture.

Beginning in February 2005, a laboratory technician was added to each mobile outreach team, and rapid syphilis testing was offered to all FSW during that eight-week screening cycle. In subsequent intervention cycles, Determine Syphilis TP testing was offered to FSWs who had not been tested in the previous 16 weeks. In total, 3682 FSW were offered syphilis

Abbreviations: CT, chlamydial infection; FSW, female sex workers; GC, gonorrhoea; PCR, polymerase chain reaction; PPV, positive predictive values; PROCETSS, Peruvian Ministry of Health HIV/STI Control Program; RPR, rapid plasma reagin; STI, sexually transmitted infections; TPHA, *Treponema pallidum* haemagglutination assay; TPPA, *Treponema pallidum* particle agglutination assay; TV, trichomoniasis

Table 1 Participation rates and syphilis prevalence diagnosed by Determine Syphilis TP, rapid plasma reagin (RPR) and *Treponema pallidum* haemagglutination assay (TPHA) using whole blood among 3682 female sex workers (FSW) in 10 cities in Peru

		Participation rate		Determine positive		RPR reactive		RPR reactive and TPHA positive		RPR ⩾1:8 and TPHA positive		RPR ⩾1:16 and TPHA positive	
City	FSW approached	n	%	n	%	n	%	n	%	n	%	n	%
Cajamarca	394	391	99.3	4	1.0	10	2.6	10	2.6	0	0.0	0	0.0
Cerro de Pasco	318	308	96.9	5	1.6	6	1.9	3	1.0	1	0.3	1	0.3
Chincha	426	426	100.0	14	3.2	17	3.8	14	3.2	2	0.5	1	0.2
Cusco	456	456	100.0	4	0.9	11	2.4	11	2.4	3	0.7	2	0.4
Huanuco	335	331	98.8	19	6.1	24	7.7	22	7.0	7	2.2	3	1.0
Ica	321	321	100.0	10	3.2	26	8.3	23	7.3	1	0.3	0	0.0
Juliaca	390	358	91.8	0	0.0	12	4.1	7	2.4	0	0.0	0	0.0
Piura	404	373	92.4	28	7.9	23	6.5	22	6.2	2	0.6	0	0.0
Pucallpa	387	371	95.9	13	3.6	51	14.1	48	13.3	8	2.2	3	0.8
Tumbes	251	251	100.0	1	0.4	18	7.2	18	7.2	1	0.4	0	0.0
Total	3682	3586	97.4	98	2.8	198	5.7	178	5.1	25	0.7	10	0.3

tests during the first two screening cycles from February to May 2005.

Before implementation, laboratory technicians from each of the 10 intervention cities attended a full day workshop in Lima for training. The technicians practised fingerstick sample collection and rapid testing on different dilutions of serum and whole blood rapid plasma reagin (RPR) reactive and non-reactive samples. After training, the technicians accompanied the PREVEN mobile outreach teams into the field to administer the Determine Syphilis TP rapid test at sex work venues, which included bars, nightclubs, brothels and truck stops.

After giving oral consent, FSW underwent fingerstick and venepuncture to provide blood samples. The Determine Syphilis TP test was performed in commercial sex venues according to manufacturer's instructions. Briefly, the second drop of whole blood was applied directly to the sample pad followed by a drop of buffer, and read using a headlamp for supplemental light approximately 15–20 minutes after application. To be considered a valid test, a red line had to be present in the control window, and a red line in the patient window defined a positive result.

Frozen sera were subsequently shipped to a central laboratory in Lima for syphilis testing using qualitative RPR with titration when reactive. *Treponema pallidum* haemagglutination assay (TPHA) was performed on all sera from participants with reactive RPR results. Participants who tested positive in the field by Determine were referred to local health clinics to receive free treatment (three weekly doses of 2.4 MU of penicillin benzathine G), consistent with national STD management guidelines.

Table 2 Sensitivity, specificity and positive predictive value (PPV) of the Determine Syphilis TP rapid test using whole blood in the field, compared to different thresholds of serum rapid plasma reagin (RPR) reactivity and *Treponema pallidum* haemagglutination assay (TPHA) positive as the gold standard

	Gold standard					
	Serum RPR reactive and TPHA positive		Serum RPR ⩾1:8 and TPHA positive		Serum RPR ⩾1:16 and TPHA positive	
	Yes	No	Yes	No	Yes	No
Determine positive in whole blood	70	28	16	82	7	91
Determine negative in whole blood	108	3277	9	3376	3	3382
Total	178	3305	25	3458	10	3473
Sensitivity	39.3%		64.0%		70.0%	
Specificity	99.2%		97.6%		97.4%	
PPV	71.4%		16.3%		7.1%	

RESULTS

Among the 3682 FSW who were offered the rapid syphilis test, 3586 (97.4%) agreed to fingerstick and 3483 (97.1%) also provided venous blood. Of the few who declined rapid testing, more than half reported having had a recent syphilis test as their reason for not participating.

Ninety-eight whole blood samples (2.8%) obtained by fingerstick were positive by Determine Syphilis TP performed in commercial sex venues (table 1). Only 11 tests (0.3%) were interpreted as invalid, with 10 occurring in the same city and all during the first weeks of study implementation. One hundred and ninety-eight specimens (5.7%) were RPR reactive using serum tested in a central laboratory in Lima; although 178 (90%) of these RPR-reactive sera were confirmed by TPHA, only 25 (0.7% of the total) were RPR reactive at ⩾1:8 dilutions, most likely indicative of active syphilis. Overall syphilis seroreactivity rates ranged from 1.9% in Cerro de Pasco to 14.1% in Pucallpa, consistent with regional differences between cities in syphilis seroprevalences, which have shown higher rates in the jungle than in the highlands.[1 4]

Sensitivity, specificity and positive predictive value (PPV) of the Determine Syphilis TP test, on whole blood obtained by fingerstick and tested by laboratory technicians in the field, using serum RPR reactivity at any dilution confirmed by TPHA as the gold standard, were 39.3%, 99.2% and 71.4%, respectively (table 2). When using serum RPR ⩾1:8 confirmed by TPHA as the gold standard, sensitivity of the Determine test on fingerstick whole blood improved to 64.0% and to 70.0% when using RPR ⩾1:16. When the Determine Syphilis TP test was performed at the central laboratory in Lima on the 178 RPR reactive sera confirmed by TPHA, 172 (97%) tested positive by the rapid test.

Among the 98 women who tested positive by Determine Syphilis TP in the field, 86 (87%) visited the local health centre for treatment, and nearly two-thirds (55; 64%) completed the three-dose treatment regimen (fig 1). Among those for whom treatment was not prescribed, 18 (21%) had documentation of previous diagnosis and treatment of syphilis with current low RPR dilutions and 5 (5.8%) had non-reactive RPR results at the local clinic.

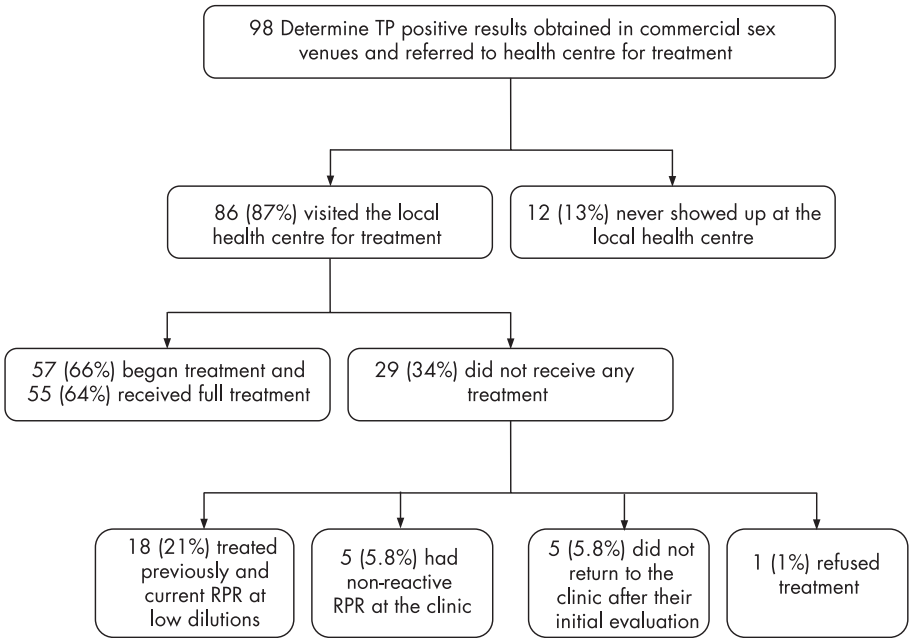

Figure 1 Flow chart illustrating treatment follow-up rates among 98 Peruvian female sex workers who tested positive for syphilis by Abbott Determine TP in commercial sex venues. RPR, rapid plasma reagin.

DISCUSSION

To our knowledge, this study provides the first field evaluation of the Determine Syphilis TP rapid test using whole blood and performed in commercial sex venues. Performance of the test in the field was substantially less sensitive than reported in previous studies, such as those reported in this journal supplement that were clinic-based and which used serum in tests performed in a laboratory[9]; sensitivity was higher in relation to sera that were RPR reactive at higher dilutions.

In a multi-laboratory based evaluation of six rapid syphilis test kits, the Determine Syphilis TP test using serum had the highest κ value, with a sensitivity and specificity of 97.2% and 94.1%, respectively, when compared with TPHA (BioMérieux, France) as the gold standard.[7] Also using serum tested in a laboratory, Diaz found comparable sensitivity (95.6–98.4%) and slightly higher specificity (95.7–97.3%) rates in Rio de Janeiro, Brazil using the same gold standard.[10] Sensitivity was 93.6% and specificity 92.5% in a laboratory-based evaluation in Sao Paulo when using sera with Venereal Disease Research Laboratory reactivity confirmed by a treponemal test as the gold standard.[11] Lien reported 99.3% agreement between the Determine Syphilis TP and the Serodia *T pallidum* particle agglutination test testing serum, plasma and whole blood in a Ho Chi Minh City laboratory.[12] In a clinical setting in San Francisco,[13] 100% sensitivity and specificity was obtained using Determine Syphilis TP on whole blood collected by fingerstick in heparinised capillary tubes,[13] suggesting that collection of whole blood by fingerstick in heparinised capillary tubes may improve sensitivity of the Determine Syphilis TP rapid test, and we have adapted this approach in continuing the programme.

Operationally, the Determine Syphilis TP rapid test was relatively easy to adapt, implement and integrate into existing worksite-based STI prevention services, and was well received by female sex workers. Inadequate lighting at some of the field sites could have contributed to missed weak positives and is a limitation in this testing environment. Although external quality assessment was not conducted during the study, the field-testing was completed within 16 weeks of the training period; tests included an internal control, and the number of invalid tests was very low. We did not use heparinised or EDTA capillary tubes for collection of blood, but instead let the second drop of fingerstick blood flow directly onto the immunochromatographic strip (ICS) pad. Subsequent review of the pads revealed that each was completely covered by blood. An alternative explanation for false-negatives in the population of FSW with high rates of previously treated syphilis results could be related to the large proportion of samples that were reactive only at low titres. Oshiro *et al* reported that samples with low levels of antibodies required a longer time period to test positive by the Determine Syphilis TP test.[14] Although the majority of FSW who tested positive completed the three-dose treatment schedule, we observed attrition from diagnosis to treatment at the local health centre, particularly among women who had been treated before and refused further treatment.

Like the TPHA or the *T pallidum* particle agglutination assay (TPPA), rapid syphilis tests are designed to detect treponemal antibodies. These antibodies persist for many years. Thus the test cannot be used to distinguish active syphilis from past treated infections. In areas where RPR testing is not available, these tests can be used to increase access to testing. In order to take full advantage of rapid diagnostic tests, studies must evaluate their utility and acceptance in clinics and field-based settings where they are to be used. In particular, it will be important to determine their cost-effectiveness in settings where a substantial proportion of the target population have been previously tested and treated. Many studies evaluating their effectiveness have been laboratory-based and have tested serum, rather than whole blood. Our findings indicate relatively low sensitivity of the Determine Syphilis TP test, which may miss a high proportion of whole blood specimens from which serum is reactive by RPR only at low titres, but may detect a higher proportion of active syphilis infections in difficult to reach, high risk populations that would otherwise be overlooked altogether.

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